



Title

The polymorphic form A of 4-[6-acetyl-3-[3-(4-acetyl-3-hydroxy-2-propylphenylthio)propoxy]-2-propylphenoxy]butyric acid.

[0001] Background of the Invention

[0002] Field of the Invention

[0003] The polymorphic form A, as defined by powder x-ray diffraction, of 4-[6-acetyl-3-[3-(4-acetyl-3-hydroxy-2-propylphenylthio)propoxy]-2-propylphenoxy]butyric acid has high solubility and bioavailability compared to other crystalline forms.

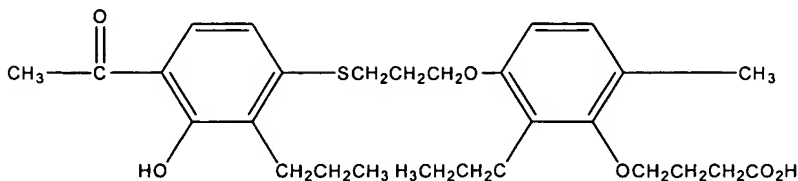
[0004] Description of the Background

[0005] Leukotrienes are metabolites of arachidonic acid through the 5'-lipoxygenase pathway and are important mediators of allergic response, such as that involved in bronchial asthma. Drugs that exert antagonistic effects on the leukotrienes are useful for the treatment of allergic diseases.

[0006] The synthesis and biological activity of many phenoxyalkylcarboxylic acid derivatives, which are leukotriene antagonists, are described by Ohashi et al., U.S. 4,985,585. The compounds were obtained in laboratory scale amounts by silica-gel column chromatography of the crude product mixtures. The solvent was evaporated to give either a pale yellow oil or colorless crystals and no deliberate effort was made to control crystal morphology.

[0007] We have observed that 4-[6-acetyl-3-[3-(4-acetyl-3-hydroxy-2-propylphenylthio)propoxy]-2-propylphenoxy]butyric acid (1), which is Example 33 in Ohashi et al., is orally active for treatment of asthma and allergic diseases and that the solid compound can crystallize into several distinct polymorphs when prepared in bulk. It

has been discovered that the crystallization conditions, particularly temperature, is critically important for preparing the different polymorphs.

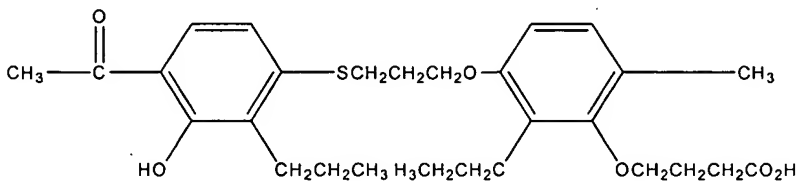


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[0008] We have also found that the solubility and the bioavailability of one of these polymorphs, identified as orthorhombic crystals (Form V in Table 1, and Form A in Fig 6), is superior to the other polymorphs and thus form A offers improved solid formulations.

Summary of the Invention

[0009] The present invention provides a pharmaceutical composition comprising a compound of formula (1) in a selected crystalline form:

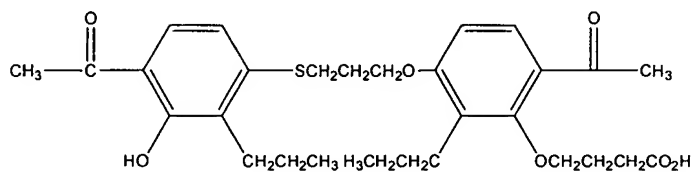


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together with a pharmaceutically acceptable carrier or excipient, wherein the selected crystalline form is composed of polymorphic form A, substantially free of undesired polymorphs. By “substantially free” is meant that little or no undesired polymorphs are detectable by powder X-ray diffractometry (PXRD). Typically, the polymorphic purity is greater than 90% (defined by peak heights in the powder x-ray diffraction trace). Preferably, the desired crystalline form of the invention is at least about 95% of the polymorphic form A (Fig. 6) as measured by relative peak heights in the region of 9° 2-theta.

[0010] The present invention also provides a process for obtaining form A of the compound of formula (1) in at least about 90% purity with respect to other polymorphs. An exemplary crystallization process includes the steps of dissolving compound (1) in 5 to 10 parts by weight of warm ethanol and 1 – 10 parts of water, agitating the resulting suspension at 20-25 °C for 15 – 60 minutes and then cooling to 5-10 °C for an additional period of 1 - 4 hours, adding 5 – 15 parts of water, agitating the mixture at 5-10 °C for an additional 1 - 4 hours, and isolating crystals of compound (1) containing at least about 90% by weight of form A (Fig. 6).

[0011] Accordingly, a pharmaceutical composition is provided, which comprises a compound of formula (1) in solid form:

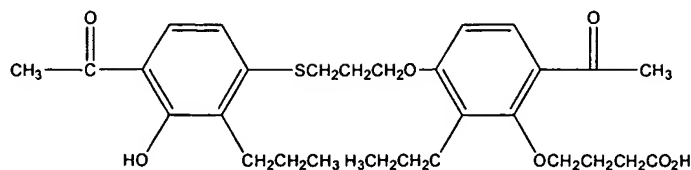


(1)

together with a pharmaceutically acceptable carrier or excipient,

provided that the compound of formula (1) is present in polymorphic Form A and is substantially free of other polymorphic forms. In a preferred embodiment of the invention, the compound of formula (1) is present as orthorhombic crystals. Also the invention can be made into the form of a tablet or capsule. Preferably, the composition of the invention gives rise to a PXRD pattern substantially as shown for polymorphic Form A in Figure 6. Moreover, it is preferably that at least about 90% of the compound of formula (1) is polymorphic Form A, as defined by PXRD peak heights around 9° 2-theta. The composition may further comprise lactose and microcrystalline cellulose. The tablet can have different weights, for example, between about 250 and about 500 mg.

[0012] The present invention is also directed to a composition comprising isolated crystals of the compound of formula (1)



(1)

in which the isolated crystals of compound (1) are present in polymorphic Form A and substantially free of other polymorphs. In a preferred embodiment the isolated crystals of compound (1) are present as orthorhombic crystals. The isolated crystals of compound (1) of the present invention preferably exhibit a PXRD pattern substantially as shown for polymorphic Form A in Figure 6. More preferably, the isolated crystals of the invention are at least about 90% polymorphic Form A, as defined by PXRD peak heights around 9° 2-theta. The invention also provides a composition having isolated crystals of compound (1), which composition contains at least about 90% of polymorphic Form A with respect to other polymorphic forms.

[0013] Brief Description of the Figures

Fig. 1 Powder X-ray Diffraction Pattern and DSC Chart of Form I

Fig. 1a DSC Chart of Form I

Fig. 2 Powder X-ray Diffraction Pattern and DSC Chart of Form II

Fig. 3 Powder X-ray Diffraction Pattern and DSC Chart of Form III

Fig. 4 Powder X-ray Diffraction Pattern and DSC Chart of Form IV

Fig. 5 Powder X-ray Diffraction Pattern and DSC Chart of Form V

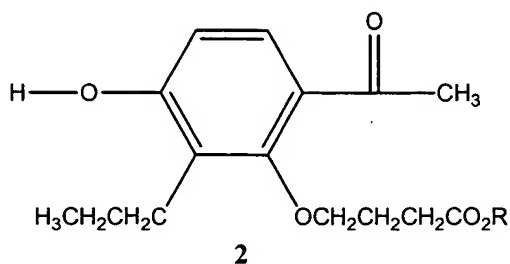
Fig. 6 X-ray diffraction patterns of three polymorphs.

Fig. 7. Schematic process for dry granulation

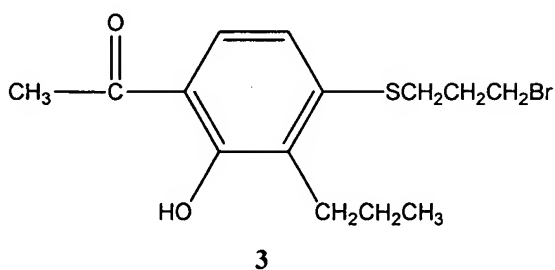
Fig. 8. Schematic process for wet granulation

[0014] Detailed Description of the Invention

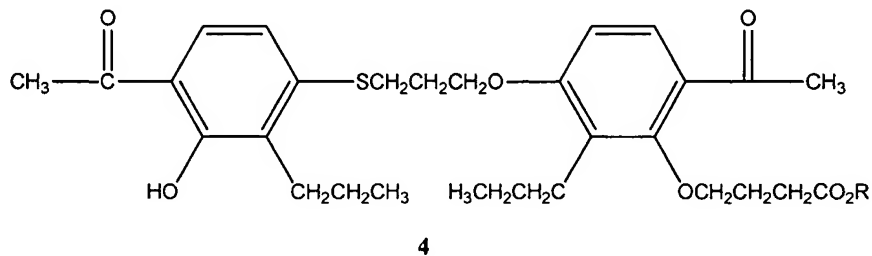
[0015] Ester (4) can be synthesized by reacting a phenol of formula (2):



wherein R is an acid protecting group, such as methyl or ethyl, with the bromo compound of formula (3):



in an organic solvent, for example acetone, methylethylketone, diethylketone or dimethylformamide. The reaction may be conducted from below room temperature up to the reflux temperature of the solvent, in the presence of an inorganic base, e.g., potassium carbonate or sodium carbonate. The addition of potassium iodide is also recommended. Analogues of compound (3) having alternative leaving groups, such as chloro and tosylate, may be used to effect the coupling reaction.



[0016] Removal of the acid protecting group by alkaline ester hydrolysis and extractive work-up gives compound (1) as a white solid.

[0017] Recrystallization of the white solid to give essentially pure form A crystals (Fig. 6), (e.g., 90% or more, preferably at least 95%) can be accomplished by dissolving compound (1) in 5 to 10 parts by weight of ethanol at 25 – 40 °C to give a yellow to orange solution. The ethanol solution is charged with 1 – 10 parts of water and agitated at 20-25 °C for about 15 – 60 minutes and then at 5-10 °C for an additional period of 1-4 hours, preferably 2.0 – 3.0 hours, resulting in an off-white suspension.

[0018] To this suspension is added 5 – 15 parts of water and the mixture is agitated at 5 - 10 °C for an additional 1 - 4 hours, preferably 1.5 – 2.0 hours. A solid, white to off-white product is isolated by vacuum filtration and the filter cake is washed with water and dried in a vacuum at 25 - 40 °C for 12 - 24 hours.

[0019] Other recrystallization conditions are also able to produce form A, such as dissolving compound (1) in a lower alcohol (isopropanol), and cooling the solution form crystals.

[0020] Therapeutic Formulations

[0021] Pharmaceutical compositions containing the orthorhombic form of compound (1) may be formulated for oral administration with inert excipients, such as a starch binder excipient, alone or in combination with microcrystalline cellulose and a suitable lubricant. Other suitable excipients include polyvinylpyrrolidinone, gelatin, hydroxy cellulose, acacia, polyethylene glycol, mannitol, sodium chloride, sodium citrate or any other excipient known to those of skill in the art of pharmaceutical compositions.

[0022] Excipients in tablets are generally classified according to their function, such as diluents (also called bulking agents and fillers), binders which hold the ingredients together in the compressed tablet, disintegrants which help facilitate the break-up of the tablet when placed in a fluid environment to release the active ingredient, and lubricants to improve the release of the compressed tablet from the die and punches. In addition,

tablets may contain other substances intended to improve the tableting process, such as flow additives, flavors, sweeteners and anti-oxidants

[0023] Tableting and some capsule filling operations are based on the ability of certain powders to bind under compression. Compressed tablets may be prepared by wet granulation, dry granulation, or direct compression. The wet granulation process includes mixing the components in powder form, preparing the granulating binder solution, thoroughly mixing the components with the granulating binder solution to form a dough, coarse screening the mass through a sieve, drying, grinding, adding the lubricant and compressing the tablets from the resulting mixture.

[0024] A preferred tablet formulation is a wet granulation containing polymorphic form A of compound (1) lactose regular, microcrystalline cellulose 101, croscarmellose, magnesium stearate and purified water, coated with Opadry II white. The tablets should weigh from 100 mg to 1000 mg, preferably 250 mg to 500 mg.

[0025] Dry granulation involves the steps of mixing the powder components, compressing the mixture into hard slugs, grinding the slugs into desired particle size, screening, adding other excipients if necessary, and compressing the mixture into tablets. The most economical tableting method, direct compression, requires only two steps, mixing the dry components and compressing the mixture into tablets.

[0026] Suitable direct compression binders include microcrystalline cellulose, compressible sugars, certain calcium salts, lactose and dextrose. Of these, microcrystalline cellulose is preferred. That excipient also displays good disintegration properties. Other good binders include calcium phosphates and compressible sugars. Calcium salt binders generally require the use of disintegrants. Mannitol and sorbitol have certain taste advantages, but they lack binding properties and require a disintegrant.

[0027] The tablets typically exhibit a tablet hardness of greater than 2 kilopond (kp)/cm.², more preferably a tablet hardness of greater than 5, most preferably about 10 to about 20 kp/cm.² and a disintegration time of less than 30 minutes, more preferably less than 15 minutes as measured utilizing the standard USP disintegration test in water.

[0028] The polymorphic form A of compound (1) may also be formulated in capsules. Solid carriers include starch, lactose, calcium sulfate, di-hydrate, teffa alba, magnesium stearate or stearic acid, talc, pectin, acacia, agar or gelatin. The carrier may also include a sustained release material such as glycerol monostearate or glycerol distearate, alone or with a wax. The amount of solid carrier varies but, preferably, will be between about 20 mg to about 1 gram per dosage unit.

[0029] Encapsulation can be done in any suitable manner, typically by use of a polymer coating used for microencapsulation, enteric coatings, multiple coatings, and the like. The polymer coating may resist disintegration upon contact with the saliva but instantly release the compound upon contact with gastric juice in the stomach, in order to control the taste of the composition. Alternatively, the polymer coating may be one that resists rapid disintegration in the presence of gastric juice. Suitable coating polymers include biodegradable polymers such as polylactic acid, polyglycolic acid, copolymers of lactic and glycolic acid, polyorthoesters, and polyanhydrides thereof. The compound also can be encapsulated by a polymer coating such as a polysaccharide (e.g., methyl or ethyl cellulose) or within a liposomal delivery system. Suitable methods of preparing compositions containing microencapsulated active ingredients are described, for example, in U.S. Patents 4,462,982, 4,710,384, 5,178,878, and 5,709,886. Preferably, the microencapsulated compounds have a mean particle size of about 50 microns to about 120 microns (e.g., about 70 microns to about 100 microns).

[0030] Typical doses of compound (1) in tablets and capsules are from about 1.0 mg/kg to about 100 mg/kg. Administration intervals vary with the patient's age, weight and general condition. In general, the drug is administered from one to four times daily.

[0031] EXAMPLES

[0032] In general, tablets are formed utilizing a carrier such as modified starch, alone or in combination with 10% by weight of carboxymethyl cellulose (Avicel). The formulations are compressed at from 1,000 to 3,000 pounds pressure in the tablet-forming process. The tablets preferably exhibit an average hardness of about 1.5 to 8.0 kp/cm.^{sup.2}, preferably 5.0 to 7.5 kp/cm². Disintegration time varies from about 30 seconds to about 15 or 20 minutes. The following examples give specific embodiments of the invention but should not be construed as limiting its scope.

[0033] EXAMPLE 1

[0034] Synthesis of ethyl 4-[6-acetyl-3-[3-(4-acetyl-3-hydroxy-2-propylphenylthio)-propoxy]-2-propyl phenoxy]butyrate

[0035] To a stirred mixture of ethyl 4-(6-acetyl-3-hydroxy-2-propylphenoxy)butyrate (1.6 g), potassium iodide (0.5 g) and potassium carbonate (1.45 g) in acetone (30 ml) was added drop wise a solution of 4-(3-bromopropylthio)-2-hydroxy-3-propylphenyl - ethanone (1.9 g) in acetone (10 ml) with heating to reflux. After refluxing six hours the mixture was cooled to room temperature and inorganic materials were separated by filtration. The filtrate was concentrated and the residue was separated and purified by silica-gel column chromatography (eluting with benzene:ethyl acetate=9:1) to give the title compound as crude crystals (2.1 g, 72.4%) which were recrystallized from ethanol to give colorless crystals, mp 65-66 °C.

[0036] EXAMPLE 2

[0037] Synthesis of 4-[6-acetyl-3-[3-(4-acetyl-3-hydroxy-2-propylphenylthio)propoxy]-2-propylphenoxy]butyric acid

[0038] To a mixture of ethyl 4-[6-acetyl-3-[3-(4-acetyl-3-hydroxy -2-propylphenylthio)propoxy]-2-propylphenoxy]butyrate (2.1 g) in ethanol (10 ml) was added a solution of sodium hydroxide (0.26 g) dissolved into water (10 ml). After heating on a hot water bath for 5 minutes, the mixture was cooled by adding ice-water and was made acidic by addition of hydrochloric acid, followed by extraction with ethyl acetate. The organic layer was washed with water, dried over sodium sulfate and concentrated. The resultant residue was separated and purified by silica-gel column chromatography (eluting with ethanol:methylene chloride=3:100) to give the title compound (1.3 g, 65.2%) as colorless crystals, mp 79-81 °C.

[0039] EXAMPLE 3

[0040] Crystalline polymorphism

[0041] After re-crystallization with individual solvents, compound (1) was subjected to powder X-ray diffractometry, thermal analysis and determination of solubility in ether; thus an exploratory evaluation of the crystalline polymorphism was made. The results demonstrate that compound (1) is present in 5 different crystalline polymorphs.

[0042] Figures 1 - 5 show the powder X-ray diffraction patterns and DSC for metastable crystal types I through V. Table 1 shows the preparatory procedures for types I through V and their solubility in ether.

Table 1 Preparation of Crystalline Polymorphs and Their Solubilities in Ether

Crystal form	Preparatory procedures	Solubility (mg/mL)
I	After compound (1) was heated and dissolved in a 4-fold quantity of isopropyl ether, the resultant solution was allowed to cool at room temperature (crystallization took place in the vicinity of 40 °C). Alternatively, after the compound was heated and dissolved in a 5-fold quantity of acetonitrile, the resultant solution was maintained at 40 °C in an incubator.	36.7

II	After compound (1) was heated and dissolved in a 10-fold quantity of acetonitrile, the resultant solution was cooled and agitated in an ice water bath.	40.5
III	After compound (1) was heated and dissolved in a 10-fold quantity of acetonitrile, the resultant solution was maintained at 25 °C in an incubator.	35.3
IV	After compound (1) was heated and dissolved in a 5-fold quantity of ethanol, a 2.5-fold quantity of water was added thereto while hot, which was then allowed to cool at room temperature.	45.8
V	After compound (1) was heated and dissolved in a 5-fold quantity of ethanol, the resultant was cooled and agitated in an ice water bath, and a 2.5-fold quantity of water was added thereto while cold. Alternatively, compound (1) was heated and dissolved in a 3.5-fold quantity of isopropanol and the resulting solution was maintained at 0 °C in a refrigerator.	47.6

[0043] Table 1 shows that the crystallization temperature was critically important in preparing the various crystalline polymorphs. When the bulk ingredient is prepared, crystallization takes place on a large scale and failure in controlling the exact temperature can result in a mixture of stable and metastable crystals, giving a larger variance in the physicochemical properties and bioavailability among production lots, against which precautions should be taken..

[0044] EXAMPLE 4

[0045] Bulk crystallization procedure for obtaining orthorhombic polymorph, crystal type V (Form A).

[0046] Off-white solid compound (1) 34g was dissolved in 204 mL (6 parts wrt mass of dry filter cake) of ethanol (40 °C) giving a yellow to orange solution. With moderate agitation, the ethanol solution was charged with 43 mL (1.3 parts) of water. The reaction mixture was cooled to 20 – 25 °C and agitated at 20-25 °C for about 15 minutes and then at 10 - 15 °C for an additional period of 1-2 hours, appearing as an off-white suspension.

[0047] To the resulting suspension was then charged 364 mL (10.7 parts) of water and the mixture was agitated at 5-10 °C for an additional 1-2 hours. A solid, white to off-white product was isolated by vacuum filtration. The filter cake was washed with 2x30 mL of water. The off white solid was dried in a vacuum at 35-40 °C for 24 hours.

[0048] EXAMPLE 5

Solubility data of compound (1) in ethanol/water (2:1)

temperature	desired polymorphic form V (form A)	undesired monoclinic polymorph
22°C	6.7g/L	3.4 g/L
30°C	15.7g/L	6.1 g/L
40°C	46g/L	17.2 g/L

[0049] Samples of compound (1) (5g) were suspended in ethanol/water (2:1, 100 mL) and stirred for one hour at temperatures of 22°C, 30°C, and 40°C, respectively. The suspensions were filtered and the solids dried in a vacuum oven at room temperature overnight to give the insoluble material. The solubilities were calculated by subtractive means based on recovered material.

[0050] EXAMPLE 6

[0051] In general wet granulation tablets were prepared with a binding solution comprised of an aqueous solution of hydroxypropylcellulose. Granulation was performed with a high shear granulator, the resultant wet mass was fluid bed dried, milled, blended with extragranular excipients to aid disintegration, flow and compressibility, and subsequently tableted on a tablet press. These core tablets were film coated to standardize appearance and to improve compliance (i.e. ease of swallowing). Excipients included, but were not limited to croscarmellose sodium, magnesium stearate, hydroxypropylcellulose, hydroxypropylmethylcellulose, lactose, glyceryl behenate, polyvinylpyrrolidone, mannitol, titanium dioxide and microcrystalline cellulose.

[0052] **EXAMPLE 7**

[0053] In general, the dry granulation formulation was formed by dry blending (in a tumble blender or high shear mixer) a portion of the binding, disintegration and lubrication powders. This dry powder blend was formed into granules through the use of a roller compactor equipped with an oscillating (shear) granulator. The ss mesh screen, gap width, gap force, roller speed and granulator speeds were defined to optimize the formulation physical parameters as apparent to those skilled in the art of pharmaceutical processing. Excipients included, but were not limited to croscarmellose sodium, magnesium stearate, hydroxypropylcellulose, hydroxypropylmethylcellulose, lactose, glyceryl behenate, polyvinylpyrrolidone, mannitol, titanium dioxide and microcrystalline cellulose.

[0054] **EXAMPLE 8**

[0055] Specific formulation for dry granulation.

Table 3.4.1: Proposed initial formulation compositions for dry granulation prototyping

No.	Ingredient	Prototype 1 (mg/tablet)	Prototype 2 (mg/tablet)
1	Compound (1), Type V (Form A)	250	250
2	Lactose regular/fast flow	7.5	--
3	Microcrystalline cellulose PH101	31	31
4	Croscarmellose sodium	20	20
5	Hydroxypropylcellulose	80	--
6	Magnesium stearate	2.0	--
7	Hydroxypropylmethylcellulose 2910	8.0	--
8	Titanium Dioxide	1.0	--
9	Carnauba wax	0.5	0.5
10	Polyvinylpyrrolidone	--	85
11	Mannitol	--	3.5
12	Glyceryl behenate	--	2.0
13	Opadry II (white)	--	8.0
	Total	400 mg	400 mg

The dry granulation process is given in the chart in Fig. 7.

[0056] **EXAMPLE 9**

[0057] Specific formulations for wet granulation.

Table 3.4.2: Proposed initial formulation compositions for wet granulation prototyping

No.	Ingredient	Prototype 3 (mg/tablet)	Prototype 4 (mg/tablet)
1	Compound (1), Type V (Form A)	250	250
2	Lactose regular/fast flow	7.5	--
3	Microcrystalline cellulose PH101	32	32
4	Croscarmellose sodium	25	25
5	Hydroxypropylcellulose	25	--
6	Magnesium stearate	2.0	--
7	Hydroxypropylmethylcellulose 2910	7.0	--
8	Titanium Dioxide	1.0	--
9	Carnauba wax	0.5	0.5
10	Polyvinylpyrrolidone	--	30
11	Mannitol	--	3.5
12	Glyceryl behenate	--	2.0
13	Opadry II (white)	--	7.0
	Total	350 mg	350 mg

The wet granulation process is given in the chart in Fig. 8.

[0058] The preferred embodiments of the invention have been described above in detail. Various modifications and improvements thereto will become readily apparent to those skilled in the art. The foregoing examples are intended to be non-limiting and exemplary of the invention described in the foregoing specification and claimed below.

[0059] EXAMPLE 10 - PXRD Analysis

[0060] The samples were prepared by a normal front packing technique and run on a Siemens D5000 Diffractometer System. A high-resolution Cu-K α -source was used, operating at 50 kV/35 mA. The secondary beam was monochromatized by a Kevex solid state detector. The step scan mode was used for data collection within the range of 2.5° - 35° (2-theta). The obtained data were processed by *Diffraction Plus™* Software.

[0061] The parts of the diffraction patterns of three different polymorphs are shown in Fig. 6, determined as Form A (likely an orthorhombic structure, specified type V), Form B (I) and Form C (II) (both monoclinic lattices) are also shown.

[0062] As one can see the top pattern is quite different from the other two. The differences are clearly marked with arrows above the top trace. Most of the single peaks on the upper pattern became doublets on the other two. This strongly suggests a structural transition with lowering of the overall symmetry. In order to find out some criteria for better distinguishing of these polymorphs, an attempt for indexing the unknown lattices was performed. The results reveal an orthorhombic lattice (top trace, Form A) and a monoclinic one (middle trace, Form B). The bottom trace (Form C) has also a monoclinic lattice very similar to that one of Form B, but with some missing reflections (marked with arrows) that could result from some structural differences.

[0063] The structure of our Form A is very close to Form V in Table 1 and Fig. 5, although there are some differences at the range $19 - 25^\circ$ 2-theta. On the other hand, the diffraction patterns for polymorphs Form I and Form II match well with Forms B and C, as they all apparently show the splitting of the main reflections due to reducing the overall symmetry from orthorhombic to monoclinic.

[0064] Because crystallographic characterizations of all five polymorphs described in Table 1 are difficult to reproduce, we will characterize the structural state of compound (1) in pharmaceutical samples only by means of its appearance as Form A, as defined by PXRD.